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Original Article

Cytoreductive surgery with or without perioperative intraperitoneal chemotherapy for the management of peritoneal carcinomatosis: Our initial experience

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Abstract

Aim: We studied to present our initial experience of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) or early postoperative intraperitoneal chemotherapy (EPIC) in the treatment of peritoneal carcinomatosis.

Material and Methods: The results of 20 consecutive patients treated with CRS±HIPEC or EPIC for peritoneal carcinomatosis in our hospital between November 2014 and February 2019 were evaluated retrospectively. Demographic, clinical and histopathological data of the patients were analyzed. The patients were also divided into two groups as PCI score <10 and PCI score ≥ 10 and a comparison was made between the groups.

Results: There were 20 patients in our study. Fifteen patients were female and 5 were male. The mean age was 52.2±15.7 years. Primary tumor was ovarian cancer in 8 patients, colorectal cancer in 8 patients, malignant mesothelioma in 3 patients and gastric cancer in 1 patient. In the ovarian cancer group, CRS alone was applied in 4 patients, CRS+HIPEC in 3 patients and CRS+EPIC in 1 patient. All patients with colorectal cancer underwent CRS+HIPEC. Two of the patients with malignant mesothelioma were treated with CRS+HIPEC and one with CRS+EPIC. The patient with gastric cancer received CRS+HIPEC. The mean peritoneal carcinomatosis index (PCI) was 12.35±7.71. The median completeness of cytoreduction (CC) score was 0 (0-1). The mean operating time was 292.5±59.9 minutes. Perioperative morbidity was developed in 11 patients, and HIPEC-induced toxicity occured in 2 patients. Perioperative mortality was seen in 1 patient. The median overall survival was 17.7 (1.1-56) months. In addition, when two groups were compared, there was no statistically significant difference in terms of age, gender, origin of tumor, surgical method, CC score, operative time, Clavien-Dindo score, postoperative hospital stay and survival (p>0.05).

Conclusion: Cytoreductive surgery and intraperito<neal chemotherapy provide satisfactory results in the treatment of patients with peritoneal carcinomatosis. Good preoperative evaluation, appropriate patient selection and multidisciplinary approach are essential for the success of the curative approach to peritoneal carcinomatosis.

Keywords: Peritoneal carcinomatosis; cytoreductive surgery; HIPEC; EPIC

INTRODUCTION

Peritoneal carcinomatosis (PC) is a common clinical condition that affects long-term survival in advanced stages of peritoneal mesothelioma as well as gastrointestinal and gynecological cancers. Among this group of patients, approximately 15% of colorectal cancers (CRCs) are diagnosed with PC during diagnosis and only 6 months of survival can be achieved with palliative treatments (1). This clinical entity has been regarded as a systemic disease in the context of stereotyped perspective and until recently managed only with palliative modalities. However, Spratt (2) and Sugarbaker (3) suggested that PC could be treated as a local disease rather than a stage IV disease in the 80s and 90s. Nowadays, the spread of cytoreductive surgery (CRS) plus hyperthermic intraperitoneal chemotherapy (HIPEC) or early postoperative intraperitoneal chemotherapy (EPIC) and the positive results published have made the curative approach to PC popular.

Cytoreductive surgery is a series of organ resection and peritonectomy procedures described by Sugarbaker (3). The aim is to remove tissues, organs and peritoneal

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surfaces that involved with tumor without leaving any visible tumoral deposit in the abdominal cavity. Application of chemotherapy intraperitoneally upon completion of surgery targets microscopically cytoreduction. By giving chemotherapeutic drugs directly into the abdominal cavity, minimal inhibitory concentrations can be reached with lower doses of chemotherapeutics, with similar efficacy being achieved with less toxic and adverse events. The pharmacokinetic efficiency of intraabdominal application is higher than that of conventional systemic chemotherapy (4). High temperatures increase efficiency of intraperitoneal chemotherapy by accelerating peritoneal blood flow and with direct cytotoxicity and its effect on tumor microenvironment (5). Therefore, intraperitoneal chemotherapy is recommended to be administered at 40-42 °C, where thermal chemosensitization is in maximum (6). At the present time, intraperitoneal chemotherapy can be provided with a desired temperature and speed with high-tech devices.

A multidisciplinary management which consists of meticulous patient selection, achieving complete cytoreduction, applying intraperitoneal chemotherapy and adjuvant systemic therapies, is a must in these three basic applications with the purpose of obtaining promising results in the treatment of PC. Extensive surgery and intraperitoneal heated chemotherapy provide prolongation of survival if the right patient is selected, and enable curative approach for these patient groups who have a poor natural course (7).

In this study, our objective is to reveal the results of patients who underwent CRS with or without HIPEC or EPIC for PC in our hospital by refering to the available literature.

MATERIAL and METHODS

Between November 2014 and February 2019, prospectively recorded results of 20 consecutive patients who received CRS±HIPEC or EPIC for curative treatment in our hospital were analyzed. Preoperative staging was performed by thoraco-abdominal computed tomography (CT) and [^{18}F] fluorodeoxyglucose (FDG) positron emission tomography / computed tomography (^{18}F-FDG PET/CT). Tumor markers were studied. Resectability was assessed, and treatment strategy was determined. Indication and algoritm of management were determined in multidisciplinary oncology council. The patients who were eligible for curative surgery were selected with the aim of achieving full cytoreduction. A palliative approach was planned for patients with radiological mesenteric vasculature invasion, retroperitoneal involvement, massive pancreatic capsular invasion, small intestinal involvement that would require resection of more than 1/3 of total extent, unresectable hepatic metastasis or extraabdominal metastases and/or Eastern Cooperative Oncology Group (ECOG) performance score ≥3. The patients and their relatives were informed in detail about the application, complications, necessity of ostomy (permanent/temporary) and organ resections. General condition and nutritional status of the patients who were candidates for surgery were evaluated, and the patients required were hospitalized before surgery. Blood values and nutritional parameters were corrected and prepared for the operation. Postoperative complications were assessed according to the Clavien-Dindo classification (8), whereas HIPEC-induced toxicity was classified according to the Common Terminology Criteria for Adverse Events (CTCAE) criteria (9). All patients were evaluated regularly with CT and tumor markers during the follow-up period. During this period, recurrent disease and lost cases were identified. Patients' demographic, clinical and histopathological characteristics were reviewed retrospectively. Written informed consent was obtained from each patient for surgical intervention prior to surgery. The study was approved by the Research Ethics Committee of our insitution.

Cytoreductive Surgery

All patients underwent prophylaxis against venous thromboembolism with low-molecular-weight heparin, and were put compression socks on. A urinary catheter was inserted in all cases, and bilateral double-J ureteral stents were placed to patients with increased risk of urinary tract injury. A second-generation cephalosporin and a nitroimidazole agent were injected for antibiotic prophylaxis. Second doses were administered after 3 hours of operation. Lloyd-Davies position was given to patients on the operating table. The incision was made as a midline incision from the xiphoid to the pubis. Old midline incision scars and umbilicus were excised due to the possibility of tumoral implant. In patients requiring right or left diaphragmatic peritonectomy, the xiphoid and epigastric fat pad were excised. After abdominal opening, ascites fluid and mucin decompression were performed. Thompson retractor was used for retraction. Severity of disease was scored with Peritoneal Carcinomatosis Index (PCI) defined by Sugarbaker *et al*. (10) (Figure 1A), and intraoperative staging was performed. Cytoreduction completeness was calculated using the remaining tumor scoring system, 'completeness of cytoreduction' (CC) at the end of surgery (Figure 1B) (7). This scoring system is as follows: CC-0 was no visible PC after CRS; CC-1 was nodules persisting < 2.5 mm after CRS; CC-2 was nodules persisting between 2.5 mm and 2.5 cm; CC-3 was nodules persisting > 2.5 cm. Both CC-0 and CC-1 were regarded as complete cytoreduction for cancers of ovarian origin. However, for cancers of colorectal or stomach origin, CC-0 must be provided for complete cytoreduction. Palliative interventions (stoma, debulking, palliative resections) were performed in case of unresectability criteria that could not be detected radiologically. HIPEC was not performed in these patients, and these patients were excluded from the study.

Macroscopic complete cytoreduction was targeted in all procedures in patients who were decided to have CRS, and aggressive organ and peritoneal resections were performed.

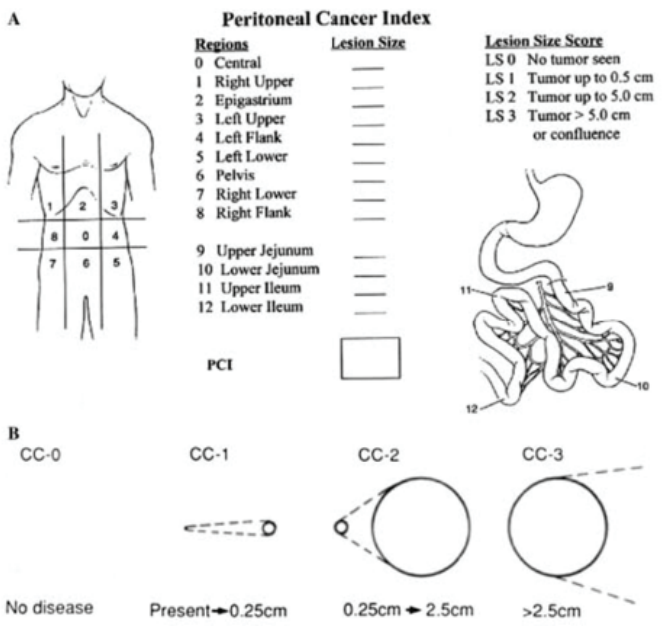

Figure 1. (A) Peritoneal Cancer Index (PCI) and (B) Completeness of Cytoreduction score (CC-s), according to Sugarbaker

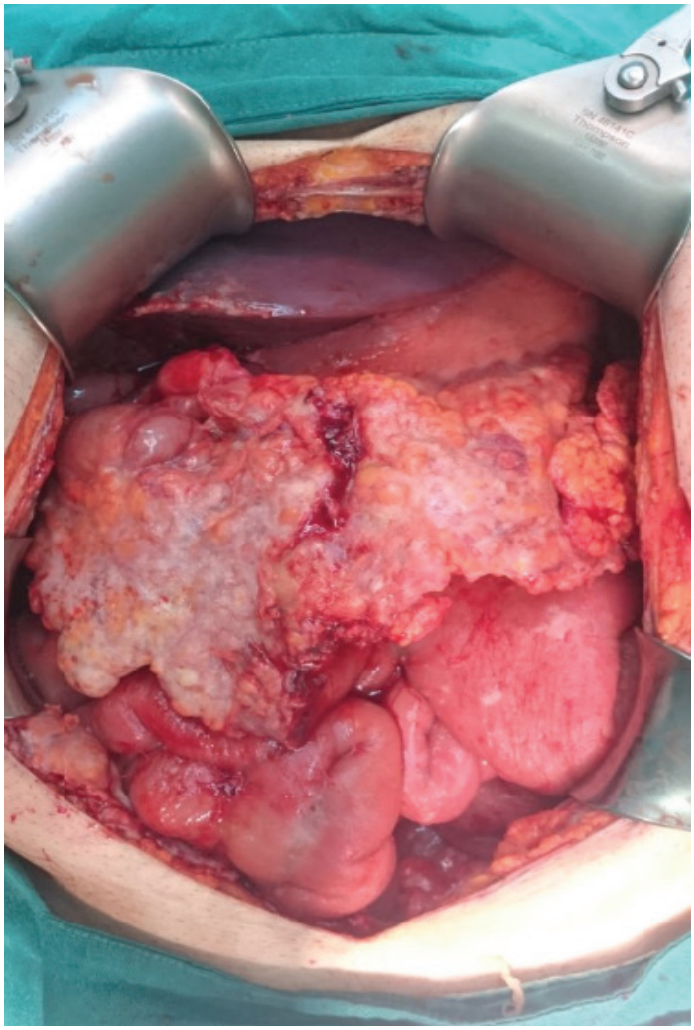

Figure 2. Intraoperative view of a patient with peritoneal carcinomatosis after midline incision

Figure 2 depicts the initial operative image of a patient with PC who underwent CRS. After exploration of the abdomen, the organs and peritoneal surfaces required to be removed were determined. Surgical strategy was established. Often omentectomy was performed first (Figure 3).

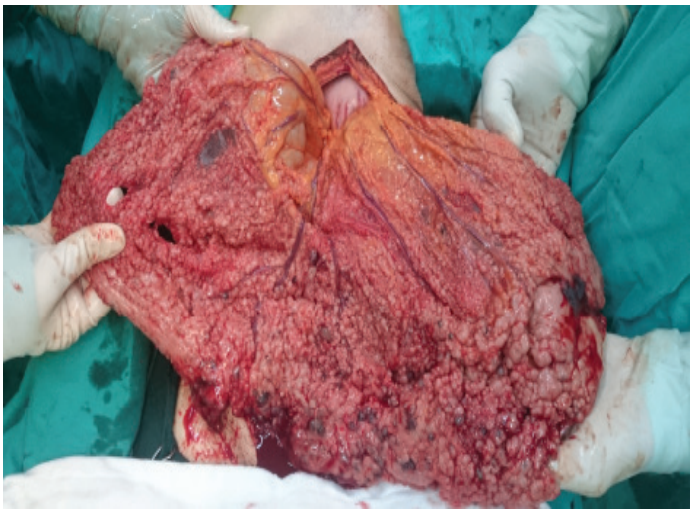

Figure 3. Omental cake in a patient who underwent total peritonectomy

Peritoneal layers were removed by peeling in all abdominal quadrants. Peritoneal stripping was not performed in peritoneal parts that did not involve the disease. Tumor nodules on the liver surface were removed by stripping off Glisson's capsule. To achieve a complete right upper quadrant diaphragmatic peritonectomy, the liver was fully mobilized and rotated medially. Diaphragmatic peritoneum was completely removed (Figure 4).

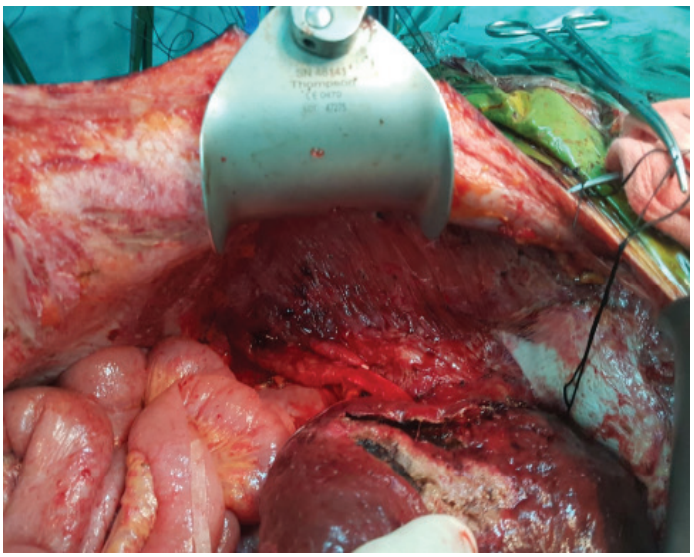

Figure 4. Completed right diaphragmatic peritonectomy and bare diaphragmatic fibers

Left diaphragmatic peritonectomy was performed in the same way. In patients with diaphragmatic injury or those requiring partial resection, the injury was repaired after

inflating the lung. Chest tube was inserted in 2 patients. Falciform ligament was removed. Cholecystectomy was performed. Hepatoduodenal ligament and lesser omentum were excised in selected cases. Lesser omentum and gastrocolic ligament were opened even without involvement to allow chemotherapy solution to reach everywhere. Splenectomy was performed in appropriate cases. Peeling of the peritoneum covering the pelvis, removal of organs such as rectum, uterus, ovaries and bladder within the pelvis were performed extraperitoneally as en bloc in patients who needed cytoreduction in the pelvis. Bilateral pelvic and para-aortic lymph node harvesting was routinely performed in ovarian PC patients (Figure 5).

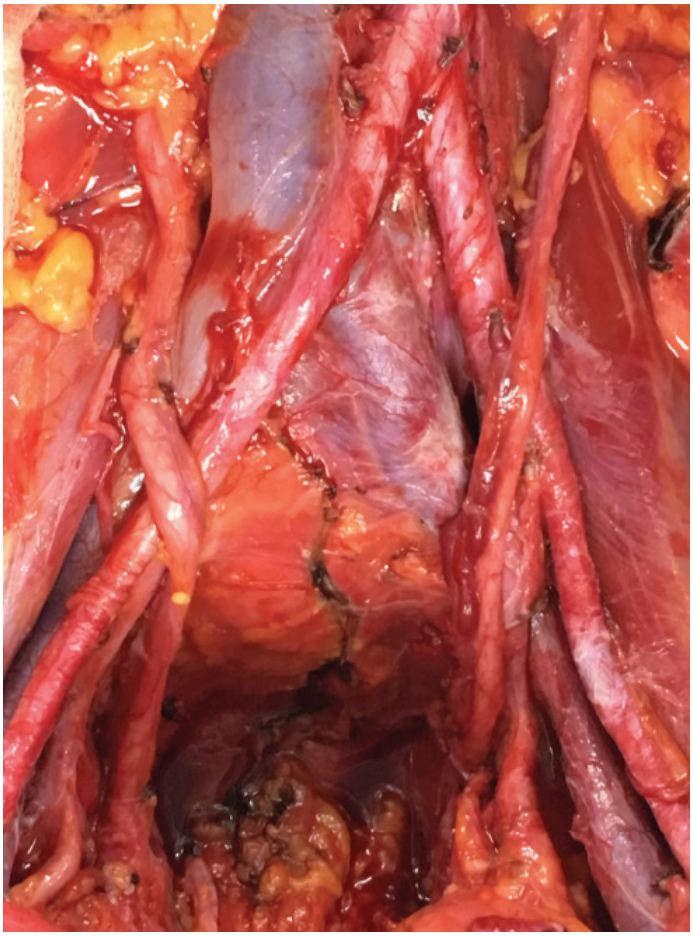

Figure 5. The left and right iliac vessels and ureters following pelvic peritonectomy and lymph node dissection

Small nodular implants in the mesentery of small bowel and colon were removed or cauterized as the final step. Some patients required partial small bowel resection in order to remove the bulky mesenteric involvement. If any part of the small bowel was resected, the anastomosis was performed before closing the abdomen for HIPEC application. In the visceral surfaces where tumor nodule resection could not be performed, excision or cauterization was used. All gastrointestinal anastomoses were done before HIPEC. In patients with requirement for an ostomy creation, the abdomen was permanently closed before HIPEC.

Hyperthermic Intraperitoneal Chemotherapy (HIPEC) After CRS, HIPEC was applied with closed technique under general anesthesia . The abdomen was closed after placing 2 inflow drains from the right side (the pouch of Douglas and subhepatic area), 2 outflow drains from the left side (superficial pelvis and splenic region) and 2 heat probes into the abdomen. Chemotherapeutic agents were put into 3-5 liters of dialysis solution according to peritoneal cavity volume and HIPEC perfusion device applied intraperitoneal chemotherapy at constant temperature of 41-43 ^{0}C for 60-120 minutes (Figure 6).

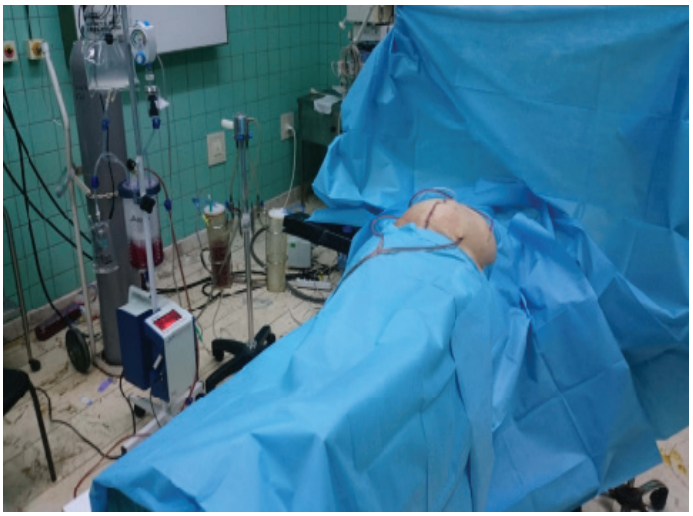

Figure 6. Appearance of patient during HIPEC application in the operating room (HIPEC: Hyperthermic Intraperitoneal Chemotherapy)

Cisplatin (50 mg/m^2) was used in 9 patients, mitomycin-C (25 mg/m^2) in 2 patients, oxaliplatin (460 mg/m^2) in 2 patients, carboplatin (350 mg/m^2) in 2 patients, and irinotecan (200 mg/m^2) in 1 patient. HIPEC perfusion solutions were prepared in the medical oncology service of our institution and were brought to the operating room (OR) by a registered chemotherapy nurse. Much attention was paid to the safety of personnel during the preparation and application of these solutions in the OR. The OR personnel and technicians were trained on this issue. Complete blood count and biochemical parameters of the patient were analysed in the mid-period of HIPEC. Both liver and kidney functions were monitored. Arterial blood gases were studied periodically and the patient's needs were monitored and met. Human albumin replacement was performed on the table in patients with low albumin levels. Erythrocyte suspension and fresh frozen plasma replacement were performed in patients who had more than six hours of operation, who underwent multiple organ resections and whose blood results were at the limit before surgery. Drains put for HIPEC into the abdominal cavity were put in placed in the patient and were removed step by step in the recovery period.

Early Postoperative Intraperitoneal Chemotherapy (EPIC)

Early postoperative intraperitoneal chemotherapy (EPIC) can be administered between days 1 and 5 postoperatively. However, abdominal lavage is performed from the day of surgery until the next day of chemotherapy, so that drains can be kept open, not blocked with debris. 1000 mL of 1.5% peritoneal dialysis solution from Tenckhoff or peritoneal dialysis catheter is rapidly introduced into the abdomen with other 3 drains closed. Then, all drains are opened without any waiting and liquid that given is taken back. This irrigation or lavage procedure is repeated every hour for the first 4 hours and then every 4 hours until EPIC begins. Then, on the first postoperative day, for example, 50 mg/m^2 cisplatin and 50 mEq sodium bicarbonate are put into a 1 liter of 1.5% peritoneal dialysis solution for patients with a body surface area less than 2 m^2 for intraperitoneal chemotherapy and 1.5 liters of 1.5% peritoneal dialysis solution for patients with a body surface area greater than 2 m^2. When other drains are in closed state, they are given rapidly by Tenckhoff or peritoneal dialysis catheter. All drains are kept closed for 23 hours so that fluid containing chemotherapeutic agent remains in the abdomen. Then, all drains are opened for 1 hour to remove unabsorbed fluid in the abdomen. This is done 5 times (11). In some cases, intraperitoneal chemotherapy is given 3 times later with 1 month interval after this treatment. This approach is not a routine procedure and is especially recommended for cases where complete cytoreduction cannot be performed on the small intestine. However, late intraperitoneal chemotherapy is often not applied in patients who have undergone extended peritonectomy because of intense adhesions in the abdomen.

Statistical analysis

Categorical variables were expressed as numbers and percentages, whereas continuous variables were summarized as mean (standard deviation) and median (minimum-maximum) where appropriate. Chi-square test (due to small expected values, exact test procedure was applied) was used to compare categorical variables between the groups. The normality of distribution for continuous variables was confirmed with the Shapiro-Wilk test. For comparison of continuous variables between two groups, the Student's t-test or Mann-Whitney U test was used depending on whether the statistical hypotheses were fulfilled or not. For univariate analysis, event free survival was calculated by Kaplan-Meier method, and Log-rank test was performed to compare the survival probabilities of two groups. All analyses were performed using IBM SPSS Statistics Version 20.0 statistical software package (IBM Co., Armonk, NY, USA). The statistical level of significance for all tests was considered to be 0.05.

RESULTS

There were 20 patients in our study. Fifteen patients were female and 5 were male. The mean age was 52.2±15.7 years. Origin of primary tumor is shown in Table 1. Primary tumor was CRC in 8 cases, ovarian cancer in 8 cases, malignant mesothelioma in 3 cases, and gastric cancer in 1 case. Treatment modalities applied to the patients are explained in Table 1. In the ovarian cancer group, CRS alone was performed in 4 patients, CRS+HIPEC in 3 patients and CRS+EPIC in 1 patient. Four patients with ovarian origin received neoadjuvant chemotherapy. The pathology of all 8 patients with ovarian cancer was serous cystadenocarcinoma. All patients with colorectal origin underwent CRS+HIPEC. Three patients with CRC underwent neoadjuvant chemotherapy. When the distribution of colorectal tumor according to localization was examined, 3 were in the rectum, 1 in the sigmoid colon, 1 in the left colon, 1 in the right colon and 1 in the cecum. One patient had synchronous primary cancers in the cecum, left colon, sigmoid colon and rectum. The pathology of all 7 patients with colorectal origin was adenocarcinoma. The pathology of one patient with left colon cancer was undifferantiated carcinoma with focal mucinous and signet-ring cell components. Two patients with malignant mesothelioma were treated with CRS+HIPEC and one with CRS+EPIC. The patient with gastric cancer received CRS+HIPEC. This patient had undergone a subtotal gastrectomy followed by adjuvant chemoradiotherapy for gastric cancer at another center 9 months before she presented to us with PC.

When all patients were divided into two groups as PCI score <10 and PCI score ≥ 10 and a comparison was made between the groups, there was no statistically significant difference in terms of age, gender, origin of tumor, surgical method, CC score, operative time, Clavien-Dindo score, postoperative hospital stay and survival (p>0.05) (Table 2). Figure 7 shows cumulative survival probabilities of two groups which were divided as PCI score <10 and PCI score ≥ 10 according to the Log-rank test. The median overall survival was 19 months (median: 1.5-36.5, 95% confidence interval [CI]) for group 1 (PCI score <10), and 19.5 months (median: 6.9-32.1, 95% confidence interval [CI]) for group 2 (PCI score ≥ 10).

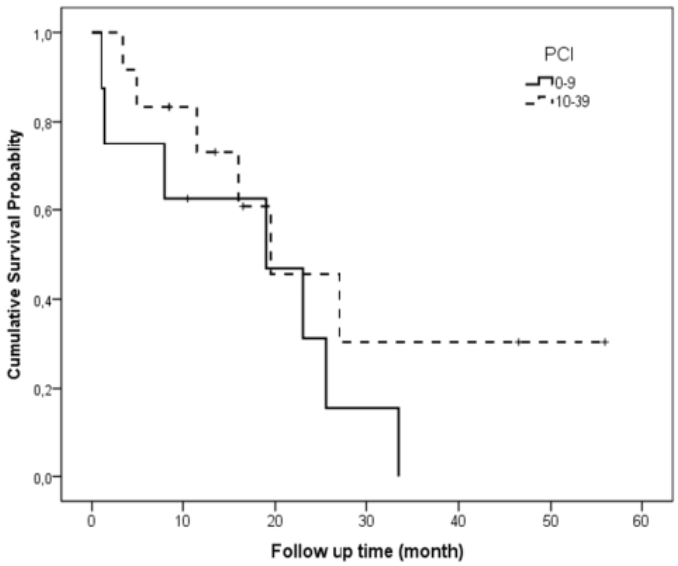

Figure 7. Cumulative survival probabilities of two groups which were divided as PCI score <10 and PCI score ≥ 10 according to the Log-rank test

Table 1. Demographic data, preoperative, peroperative and postoperative parameters of 20 patients under study

Case	Age	Gender	Origin of Primary Tumor	Treament Modality	PCI Score	CC Score	Operating Time (min)	Clavien-Dindo Grade	Postoperative Length of Stay (day)	Survival (month)
1	41	Female	Ovarian	CRS+HIPEC	23	0	360	1	8	11.5
2	35	Female	Ovarian	CRS alone	18	0	240	0	8	46.5
3	54	Female	Ovarian	CRS+EPIC	2	0	240	0	9	10.5
4	44	Female	Ovarian	CRS alone	8	0	240	0	5	19
5	53	Female	Ovarian	CRS+HIPEC	15	1	330	0	13	19.5
6	62	Female	Ovarian	CRS alone	12	1	300	0	5	16
7	43	Female	Ovarian	CRS+HIPEC	9	1	450	5	33	1.1
8	67	Female	Ovarian	CRS alone	5	0	210	0	5	25.5
9	21	Female	Rectum	CRS+HIPEC	7	0	240	1	8	23
10	70	Male	Colon	CRS+HIPEC	22	0	330	4	29	27
11	65	Male	Colon	CRS+HIPEC	10	0	270	0	7	56
12	46	Male	Rectum	CRS+HIPEC	13	0	300	3	27	5
13	56	Female	Colon	CRS+HIPEC	3	0	240	2	8	33.5
14	57	Female	Colon	CRS+HIPEC	10	0	360	2	21	13.5
15	38	Male	Rectum	CRS+HIPEC	27	0	240	3	14	16.5
16	20	Female	Colon	CRS+HIPEC	3	0	360	0	7	8
17	72	Male	Mesothelioma	CRS+EPIC	26	0	240	0	7	3.5
18	66	Female	Mesothelioma	CRS+HIPEC	10	0	300	3	40	8.5
19	71	Female	Mesothelioma	CRS+HIPEC	18	0	300	3	19	8.5
20	63	Female	Gastric	CRS+HIPEC	6	0	300	3	18	1.5

CRS: Cytoreductive Surgery
HIPEC: Hyperthermic Intraperitoneal Chemotherapy
EPIC: Early Postoperative Intraperitoneal Chemotherapy
PCI: Peritoneal Carcinomatosis Index
CC: Completeness of Cytoreduction

Operative technical data of the patients are given in Table 3. The mean PCI score was 12.35±7.71. The median completeness of cytoreduction (CC) score was 0 (0-1). The mean operating time was 292.5±59.9 minutes. Nineteen patients underwent peritonectomy in all quadrants. Diaphragmatic resection and primary repair were performed in 2 patients. Chest tube was inserted in 2 patients. The median number of resected organs was 2.8 (1-5). A total of 9 digestive anastomoses were performed in six patients. The number of patients who received a stoma was 6. The median intraoperative red blood cell (RBC) transfusions was 3.7 (2-11) units and fresh frozen plasma (FFP) 4.4 (2-10) units. In one patient who underwent CRS alone for primary ovarian cancer, the tumor was excised from the base of the liver, and massive hemorrhage developed, and 6 units of packed RBCs and 5 units of FFP were transfused intraoperatively. In another patient with recurrent ovarian cancer, an abundant bleeding occured from hepatic vein injury, liver capsule tear and parenchymal laceration, and she received 11 units of packed RBCs and 10 units of FFP intraoperatively. The mean postoperative length of stay was 14.5±10.3 days in our study.

Postoperative complications were summarized in Table 4. Postoperative morbidity was developed in 11 patients. The leading causes were respiratory complications (n=5), wound site infections (n=3), acute renal failure (n=3) anastomotic leakage (n=2), hematological complications (n=2), and intra-abdominal hemorrhage (n=1). Three patients were re-operated; the first one for second-look laparotomy with abdomino-pelvic unpacking, the second one for intra-abdominal bleeding which was controlled with primary hemostasis, and the third one for ileo-transversostomy leakage which was managed with diverting ileostomy. A Roux-en-Y esophagojejunostomy leakage was treated with endoscopic esophageal stent placement. HIPEC-induced toxicity was seen in 2 patients (10%). In a patient who was given oxaliplatin for intraperitoneal chemotherapy, febrile neutropenia and pancytopenia developed early postoperatively (CTCAE, Grade 3), and the patient was transferred to the department of hematology.

There was no the first 30-day all-cause in-hospital mortality in our study. However, there was only one perioperative mortality due to multiple organ failure on

Table 2. Demographic data, preoperative, peroperative and postoperative parameters of groups

Data	PCI Score < 10 (n=8)	PCI Score ≥ 10 (n=12)	p value
Age (year) (mean±SD)	46.0±17.7	56.3±13.4	0.156[a]
Gender			
Female	8 (100%)	7 (58.3%)	0.055[b]
Male	0	5 (41.7%)	
Tumor origin			
Ovarian	4 (50%)	4 (33.3%)	
Colon	2 (25%)	3 (25%)	
Rectum	1 (12.5%)	2 (16.7%)	0.515[b]
Mesothelioma	0	3 (25%)	
Gastric	1 (12.5%)	0	
Treatment modality			
CRS alone	2 (25%)	2 (16.7%)	
CRS+HIPEC	5 (62.5%)	9 (75%)	0.999[b]
CRS+EPIC	1 (12.5%)	1 (8.3%)	
CC score			
CC-0	7 (87.5%)	10 (83,3%)	0.999[b]
CC-1	1 (12.5%)	2 (16.7%)	
Operating time [median (min-max)]	240 (210-450)	300 (240-360)	0.343[c]
Clavien-Dindo score			
0	4 (50%)	5 (41.7%)	
1	1 (12.5%)	1 (8.3%)	
2	1 (12.5%)	1 (8.3%)	
3a	1 (12.5%)	2 (16.7%)	0.928[b]
3b	0	2 (16.7%)	
4a	0	1 (8.3%)	
4b	0	0	
5	1 (12.5%)	0	
Clavien-Dindo score (Grade 3-4-5)	2 (25%)	5 (41.7%)	0.642[b]
Postoperative length of stay (day) [median (min-max)]	8 (5-32)	13.5 (5-40)	0.305[c]
Survival (month) (median – 95% CI)	19 (1.5-36.5)	19.5 (6.9-32.1)	0.243[d]

[a] Student's t test, [b] Chi-square exact test, [c] Mann-Whitney U test, [d] Log-Rank test
SD: Standard Deviation
CRS: Cytoreductive Surgery
HIPEC: Hyperthermic Intraperitoneal Chemotherapy
EPIC: Early Postoperative Intraperitoneal Chemotherapy
PCI: Peritoneal Carcinomatosis Index
CC: Completeness of Cytoreduction
CI: Confidence Interval

the 33rd day in a patient with recurrent ovarian cancer who received CRS+HIPEC. Twelve patients were followed up with adjuvant chemotherapy. The median overall survival was 17.7 (1.1-56) months in our study. During the study period of 59.5 months, mortality was observed in 6 of 8 patients with ovarian origin, in 5 of 8 patients with colorectal origin, in one patient with malignant mesothelioma, and in one patient with gastric cancer. Of 6 patients who died of ovarian cancer, four were in CRS alone group and two in CRS+HIPEC group. One patient with malignant mesothelioma who died had received CRS+EPIC. The median overall survival was 18.7 (1.1-46.5) months in ovarian cancer group and 22.8 (5-56) months in CRC group. When all patients were divided into two groups as gynecological origin and non-gynecological origin and a comparison was made between the groups,

there was no statistically significant difference in terms of survival (18.7 *vs.* 17 months, respectively) (p>0.05). A total of 7 patients, 3 with CRC, 2 with ovarian cancer and 2 with malignant mesothelioma, are still alive without disease recurrence, and continue to be monitored in our study. When it comes to the longest survival time in our study group, we have still alive one patient with ovarian origin in her postoperative 47th month, and one patient with colorectal origin in his postoperative 56th month.

Table 3. Data of surgical procedure for the 20 patients under study

Operative Technical Data	
Mean PCI score (SD)	12.35 ± 7.71
Median CC score (range)	0 (0-1)
Mean operating time (minute) (SD)	292.5 ± 59.9
Median intraoperative RBC transfusion (unit) (range)	3.7 (2-11)
Median intraoperative FFP transfusion (unit) (range)	4.4 (2-10)
Median number of resected organs (range)	2.8 (1-5)
Total peritonectomy (n)	19
Diaphragmatic resection (n)	2
Chest tube insertion (n)	2
Gastrointestinal anastomosis (n)	9
Stoma (n)	6
Mean postoperative length of stay (day) (SD)	14.5 ± 10.35

SD: Standard Deviation
PCI: Peritoneal Carcinomatosis Index
CC: Completeness of Cytoreduction
RBC: Red Blood Cell
FFP: Fresh Frozen Plasma

Table 4. Postoperative complications for the 20 patients under study

Postoperative complication	**n**
Respiratory complications	5
Wound site infection	3
Acute renal failure	3
Anastomotic leakage	
Esophago-jejunostomy	1
Ileo-transversostomy	1
Hematological complications	
Leukopenia	1
Pancytopenia	1
Febrile neutropenia	1
Intra-abdominal hemorrhage	1
Total	**18**

DISCUSSION

Randomized controlled studies demonstrate that therapeutic surgical management of PC may improve survival in meticulously chosen patients (12,13). In the light of these results, CRS and HIPEC are increasingly used in PC treatment. This procedure has been implementing in our hospital since 2014. The limited number of patients, the heterogeneous patient population, the moderate monitoring period and the absence of long-term survival analysis are among the major restrictions of our study. The results obtained in our study of 20 consecutive patients operated on in a single institution are compatible with the publications and promising.

Multiple organ resection, prolonged operating time, HIPEC and/or EPIC as well as neoadjuvant chemotherapy, multiple prior abdominal surgeries and high ECOG scores make PC patients a candidate for complications. In our study, 35% of complications were serious complications (Clavien-Dindo; Grade 3, 4, and 5). In the literature, general morbidity due to CRS+HIPEC has been reported 12% to 56% and postoperative mortality 0% to 12% (14). The complication rates of our study are consistent with the literature. The mortality rate was 65% within our study period. We are in the opinion that this is due to lack of experience of our center and arguable nature of decisions in patient selection. Moran *et al*. reported a 18% mortality in the first 33 cases, 3% in the second 33 cases and 3% in the third 33 cases in their study of one hundred cases (15). They stated that mortality rate decreases as experience increases, and experience should be gained by whole team. In our study, when the patients were divided into two groups as PCI score < 10 and PCI score ≥ 10, and a comparison was made between the groups, we did not find any statistically significant difference in terms of overall survival between two groups. This state can be explained by small number of patients in two groups, heterogeneous patient population which included different types of tumor pathology and tumor localizations, learning curve process of our clinic, and early mortality seen in 2 patients with a PCI score < 10.

Clinical trials analyzing the effect of HIPEC in the first-line treatment for ovarian cancer have been accumulating (16). There is much heterogeneousness in chemotherapeutic agents, chemotherapy protocols, HIPEC application standards, and selecting the appropriate patient, so collection and comparison of results are very difficult. It can be inferred that there exist no conclusive proofs to advise HIPEC in ovarian cancer as part of first-line treatment other than a clinical trial. The most important factors affecting the results are PCI score and CC score. In our series, the median overall survival was 18.7 months in ovarian cancer group, and our results are consistent with the literature. In the OVHIPEC study, a phase III randomized trial from Netherlands, they provided 3 cycles of chemotherapy to the patients who were not eligible for complete cytoreduction, and the patients were subsequently operated on. The patients who received complete CRS were then divided into two categories as with or without HIPEC. It has been shown that addition of HIPEC to interval cytoreductive surgery is well tolerated and improves overall survival without recurrence in

patients with stage III epithelial ovarian cancer in the OVHIPEC study. As a result of the OVHIPEC study, addition of HIPEC to interval cytoreductive surgery showed that HIPEC prolonged median recurrence-free survival by 3.5 months and median overall survival by 11.8 months (17). In our study, 8 patients with stage III epithelial ovarian cancer who were treated with CRS alone in 4 patients, CRS+HIPEC in 3 patients, and CRS+EPIC in 1 patient, had complete cytoreduction with CC-0 in 5 patients and CC-1 in 3. The pathology of all patients with ovarian origin was serous cystadenocarcinoma. Four patients received neoadjuvant chemotherapy, and 5 patients underwent adjuvant chemotherapy. During the 59.5-month study period, 6 patients with ovarian cancer died during follow-up. The remaining 2 patients are still alive and disease-free on the 11th and 47th month, respectively. The diversity in treatment modalities which we performed in the ovarian cancer group were due to several factors such as patient preference, surgeon's choice and decision of the oncology council. All patients who are candidates for CRS are discussed in detail in the oncology council of our hospital. Intraperitoneal chemotherapy is recommended for patients whose CRS decision is taken as a result of the council decision. The application of HIPEC treatment is expensive and personally paid by the patient in our country. Besides, the high cost of HIPEC is not covered by the Social Security Institution of our country. If the patient does not want to pay the charge of HIPEC, then the patient is offered CRS + adjuvant chemotherapy or CRS + EPIC.

Large series have recently reported promising results with regard to cytoreduction plus intraperitoneal chemotherapy in terms of outcomes from oncological perspective in colorectal PC (12, 18), where almost 10% of patients come to hospital with clinical manifestations of PC. Complete cytoreduction and PCI score are the strongest factors that determine prognosis in relation to survival. When complete cytoreduction is not achieved, cytoreduction plus intraperitoneal chemotherapy do not improve survival in CRC-derived PC. In the multi-institutional study conducted by Elias *et al.*, 1-, 3-, and 5-year survival rates of all colorectal PC patients were 81%, 41%, and 27%, respectively, with a median survival of 30 months and an average hospital stay of 22.5 days (19). Overall perioperative morbidity and mortality rates were 30% and 3%, respectively. In our series, all 8 patients with colorectal origin underwent CRS+HIPEC. Three patients with CRC underwent neoadjuvant chemotherapy. A CC-0 cytoreduction score was obtained in all patients with colorectal origin. The median postoperative length of stay was 15.1 days for colorectal PC patients. Perioperative morbidity rate (Clavien-Dindo; Grade 3 and 4) was 37.5% in CRC patients, and there was no perioperative mortality. During the 59.5-month study period, 5 patients with CRC died during follow-up (62.5%). The median overall survival was 22.8 months in CRC group. Three patients from CRC group are still under follow-up and disease-free on the 56th, 17th and 14th month, respectively.

Peritoneal surface malignancies have a poor prognosis, but recently better survival rates after cytoreduction plus intraperitoneal chemotherapy have been reported for malignant peritoneal mesothelioma. In our series, 2 patients with malignant mesothelioma were treated with CRS+HIPEC and one with CRS+EPIC. Mitomycin-C (25 mg/m^2) was used for intraperitoneal chemotherapy in 2 patients and cisplatin (50 mg/m^2) in one patient. The pathology was epithelioid-type mesothelioma in 2 patients and well-differantiated papillary mesothelioma in one patient. One patient with malignant mesothelioma who died on his postoperative 4th month had received CRS+EPIC. Two patients are still alive and disease-free on the 9th month. A multicenter study analyzing CRS plus HIPEC for malignant mesothelioma in 401 patients found that the median overall survival was 53 months, and factors determining prognosis were epithelial subtype, no metastatic lymph nodes, CC-0 cytoreduction, and administration of intraperitoneal chemotherapy (20). Alexander *et al.* reported, in a multicenter trial of 211 patients with malignant mesothelioma, that the median overall survival was 38 months, and factors associated with improved survival were CC-0 or CC-1 scores and histopathological differantiation grade (21). In this study, administration of cisplatin versus mitomycin-C during intraperitoneal chemotherapy was associated with improved survival. These multicenter studies support our results in associated with CC-0 CRS.

Peritonitis carcinomatosa is encountered in 5% to 30% of patients who received potentially radical gastric cancer surgery, and the median survival achieved by systemic chemotherapy in these patients is 1-3 months (22). The function of cytoreduction plus intraperitoneal chemotherapy for cancers of stomach is still ambiguous. Glehen *et al*. found that the median survival for CRS and HIPEC in 150 cases was 9.2 months and 5-year overall survival was 13% (23). In a separate study, outcomes of 441 cases who underwent cytoreduction plus intraperitoneal chemotherapy were reviewed, the median survival was reported to be 7 months, and increased to 11 months when complete cytoreduction was performed (24). Data in the literature show that the most important factor associated with prognosis in gastric PC is complete cytoreduction. Although CC-0 CRS was performed in our single recurrent gastric cancer patient, she died of sepsis due to secondary peritonitis resulting from esophagojejunostomy leakage in spite of endoscopic stent placement followed by surgical drainage on the 50th day.

Cytoreductive surgery is an important initial step, aiming to remove all macroscopic tumor deposits to allow penetration of the adjuvant intraperitoneal chemotherapy. Perioperative intraperitoneal chemotherapy includes HIPEC and EPIC. Sugarbaker introduced the concept of EPIC in the 90s. The rationale to use EPIC includes the high risk of peritoneal recurrence, a simple surgical technique for drug delivery, and targeted effects without systemic compromise (25). It aims to enhance further intraperitoneal-targeted therapy immediately following CRS to eliminate tumor cells prior to the formation of

postoperative fibrinous adhesions (11). In the last few years, EPIC has become a less-favored option as part of perioperative intraperitoneal chemotherapy due to concerns regarding prolonged length of hospital stay, increased postoperative complications, and lack of benefits on the long-term survival outcomes of patients with PC (26-28). CRS+EPIC were performed in 2 patients in our series. EPIC was administered with carboplatin in one patient with recurrent ovarian cancer whose PCI score was 2 and cisplatin in other patient with malignant mesothelioma whose PCI score was 26. There was no postoperative complication in both patients, and the postoperative length of stay was similar for both patients (7 days *vs.* 9 days, respectively). The patient with recurrent ovarian cancer is still alive in her postoperative 11th month without disease recurrence, and continues to be monitored in our study. However, the survival was only 3.5 months for the patient with malignant mesothelioma.

Many chemotherapy drugs have been studied in CRS and HIPEC. These include a wide variety of drugs, especially cisplatin, which has increased activity at high temperatures (29). A common chemotherapeutic drug for HIPEC delivered in the management of ovarian cancer, colorectal PC and malignant mesothelioma is cisplatin. Cisplatin is the most widely used agent as a result of clinical studies (30). In our study, the most preferred drug was cisplatin. Mitomycin-C was the second one administered. Cisplatin is the most toxic drug that frequently used in the treatment. Especially nausea and vomiting, as well as nephrotoxicity are important adverse events. These toxic side effects can be managed with some precautions prior to and in time of intraperitoneal chemotherapy (31). Paclitaxel may induce bone marrow suppression. Both paclitaxel and oxaliplatin may cause neurotoxicity. In addition, all chemotherapeutic agents may increase the risk of infection (32). Among our cases, acute renal failure developed in 3 patients and bone marrow suppression occured in 2 patients. A patient with right colon cancer who was administered oxaliplatin 50 mg/m^2 for HIPEC and then developed pancytopenia and febrile neutropenia in the postoperative period was successfully treated with filgrastim, a recombinant human granulocyte-colony stimulating factor (G-CSF), in the department of hematology. Hereby, these adverse events are evaluated in the context of postoperative complications.

CONCLUSIONS

Cytoreduction and intraperitoneal chemotherapy have promising results in the treatment of PC patients. Complete cytoreduction is the most important factor for maximizing the advantage of these surgical procedures. CRS cannot be applied to every single PC patient. The patient's well-being, no extraabdominal metastasis, tumor burden permitting R0, worst-case R1 resection, achieving complete cytoreduction and application of intraperitoneal chemotherapy are the most widely used criteria in the light of available literature. Choosing the right patient and experience of the hospital are important factors that will influence oncologic outcomes as well as survival. Compared with the literature, our series with acceptable results is encouraging for this treatment, which is becoming more widespread in our country. A good preoperative evaluation, choosing the right patient and participatory approach with primary disciplines including surgical oncology, medical oncology and radiation oncology are the base of success for CRS and intraperitoneal chemotherapy in the management of carcinomatosa peritonei.

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